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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/629,551	BATHE ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *13 and 15-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/20/03,2/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-21 are pending.

Applicant's election with traverse of Group I, claims 1-12, 14 drawn to a process for the production of L-lysine, as submitted in a communication filed on 4/10/2006 is acknowledged.

Applicant's traverse is on the ground(s) that (1) there is a technical relationship that involves the same special feature, which feature defines the contribution that each of the Groups makes over the prior art, (2) the claims of Groups II-IV are all dependent on independent claim 1, and (3) the Office has not provided sufficient/adequate reasons as to why the inventions are patentably distinct, and (4) no undue burden would be imposed on the Office if all the inventions are searched in one application. These arguments are not found persuasive.

It is noted that the restriction requirement submitted was required under 35 USC 121 and not under 35 USC 121 and 372. The instant application is not the national stage of an international application. No determination as to whether there is a special technical feature linking the claimed inventions has been made because a lack of unity analysis to show the presence of different inventions is not required for applications which are not filed under 35 USC 371. In addition, the determination of whether inventions are patentably distinct does not require taking into consideration whether claims drawn to one invention are dependent upon claims which are drawn to a different invention. As set forth in MPEP 803, the criteria for a proper restriction between patentably distinct inventions requires that the inventions must be independent or distinct as claimed, and a search of all the inventions would impose an undue burden on the Examiner. Contrary to Applicant's assertions, the Examiner clearly explained the reasons why the inventions are distinct. In item 2 of the restriction requirement, the Examiner clearly indicated that the inventions of Groups I-IV were related as product and process of use but are distinct because the product of Group II can be used in three different methods (Groups I, III-IV). Thus, the

Examiner has met the requirement set forth in MPEP 806.05(h). With regard to the distinct methods of Groups I, III, IV, the Examiner indicated that these methods while using the same product (Group II) have different effects, may use other products, and comprise different steps. It is unclear to the Examiner as to how one could conclude that a method for the production of L-lysine, can have the same steps or the same effect as a method for feeding an animal, or a method of making a feed composition. Finally, arguments regarding the search of all inventions not imposing an undue burden on the Office, it is noted that each invention would require a separate patent/non/patent literature search which are not co-extensive. The search of each of the inventions would require different keywords and different class/subclass searches. Thus, contrary to Applicant's assertions, searching all the inventions would impose an undue burden on the Office.

The requirement is deemed proper and therefore is made FINAL.

Claims 13, 15-21 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-12 and 14 are at issue and are being examined herein.

Specification

1. The abstract of the disclosure is objected to for the following reasons. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. Appropriate correction is required.

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It is suggested the title be amended to indicate the particular functional characteristics associated with the L-lysine producing bacteria of the invention. Appropriate correction is required.

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/401752 filed on 8/8/2002. It is noted, however, that the instant application is in German and no English translation has been provided.

4. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to GERMANY 102 35 029.9 filed on 7/31/2002. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However, no English translation of the foreign priority document has been filed.

5. In view of the fact that the Examiner is unable to determine the contents of provisional application No. 60/401752, or the contents of the foreign priority document, the Examiner will use the filing date of the instant application, 7/30/2003, for prior art purposes.

Information Disclosure Statement

6. The information disclosure statements (IDS) submitted on 10/20/2003 and 2/23/2004 are acknowledged. The submission submitted on 2/23/2004 is in compliance with the provisions of 37 CFR 1.97 and is being considered by the examiner. The submission submitted on 10/20/2003 has not been considered by the Examiner as the references to be considered have not been provided on a separate list in compliance with 37 CFR 1.98(a)(1). Specifically, there is no list providing the pending applications for which Applicant requests consideration.

Claim Objections

7. Claim 5 is objected to due to the recitation of "one or more genes from the following group.....the pck gene...., or the gene zwa2...". The term "or" should be replaced with "and" to define the group. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 1, 6-9, 11, 14 (claims 2-5, 10, 12 dependent thereon) is indefinite in the recitation of "sensitive" for the following reasons. The term "sensitive" refers to the ability of being readily affected or changed in some way. In the absence of a definition of the term, it is unclear as to which is the effect associated with the term "sensitive" (e.g., reduced growth, increased growth). For examination purposes, it will be assumed that the term "sensitive to" reads "growth-inhibited by". Correction is required.

11. Claim 1 (claims 2-12, 14 dependent thereon) is indefinite in the recitation of "isolating L-lysine from the fermentation medium or from the bacterium, so that > 0 to 100% of the constituents from the fermentation broth and/or from the biomass are present" for the following reasons. The fermentation medium encompasses the broth as well as the biomass. The term "isolating L-lysine from the fermentation medium" implies that L-lysine is separated from the broth and the biomass. Thus, it is unclear as to how one could separate L-lysine from the broth and biomass and, at the same time, have 100% of the constituents from the fermentation broth and/or from the biomass present. For examination purposes, no patentable weight will be given to the term "so that ....are present". Correction is required.

12. Claim 4 is indefinite in the recitation of "the gene X" as there is no antecedent basis for "the gene X" in claim 1, from which claim 4 depends. For examination purposes, the term "the" will be interpreted as "a". Correction is required.

13. Claim 4 is indefinite in the recitation of "one or more of the following genes enhanced....: the gene lysC....., simultaneously the gene lysE..." as it is unclear how the term "simultaneously" should be interpreted within the context of the claim. While the preamble recites "one or more", the term "simultaneously" would imply that at least two genes should be enhanced at the same time. If this is the case, it is unclear as to which are the genes which have to be enhanced simultaneously. For examination purposes, no patentable weight will be given to the term. Correction is required.

14. Claim 12 is indefinite in the recitation of "wherein said bacterium is identified as Brevibacterium" as there is no antecedent basis for an identification step in claim 1, from which claim 12 depends. For examination purposes, it will be assumed that the term reads "wherein said bacterium is Brevibacterium". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-12 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-12 and 14 are directed to a process for the production of L-lysine comprising cultivating a L-lysine producing coryneform bacterium, *C. glutamicum* cell or *Brevibacterium* cell whose growth is inhibited in the presence of (1) any diaminopimelic acid analogue, or (2) 4-fluorodiaminopimelic acid, 4-hydroxydiaminopimelic acid, 4-oxodiaminopimelic acid, or 2,4,6-triaminopimelic acid. Claims 2 and 4 also require the L-lysine producing cell to be modified in any way such that (1) the activity of any protein

associated with the biosynthesis of L-lysine is increased, or (2) the activity of any feedback-resistant aspartate kinase, dihydrodipicolinate synthase, glyceraldehyde-3-phosphate dehydrogenase, pyruvate carboxylase, glucose-6-phosphate dehydrogenase, lysine export protein, zwa1 protein, diaminopimelic acid decarboxylase, sigma factor C, triose phosphate isomerase, and/or 3-phosphoglycerate kinase is increased. It is noted that the specification discloses the term "enhancement" to encompass the increase of the intracellular activity of a protein or enzyme in a microorganism (page 6, lines 22-29). Claims 3 and 5 also require the L-lysine cell to be modified in any way such that any metabolic pathway associated with reducing the formation of L-lysine is blocked, or the intracellular activity of the gene product of the pck, pgi, deaD, citE, menE, mikE17, poxB, and/or zwa2 endogenous gene is reduced or eliminated. It is noted that the specification defines the term "attenuation" as the reduction or switching off of the intracellular activity of one or more enzymes or proteins in a microorganism (page 8, line 27-page 9, line 5). See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are

representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The claims require any number of modifications which would result in any coryneform bacterium, *C. glutamicum* cell or *Brevibacterium* cell to be growth-inhibited by any diaminopimelic acid analog, which have not been described. In addition, the specification is silent with regard to the characteristics of any corynebacterium species which would be growth-inhibited by 4-fluorodiaminopimelic acid, 4-hydroxydiaminopimelic acid, 4-oxodiaminopimelic acid, or 2,4,6-triaminopimelic acid. Furthermore, while the claims require any number of modifications in any coryneform bacterium which would result in an increase in the intracellular activity of some proteins and the reduction/elimination of the intracellular activity of others, such as inhibitors/agonists, transcriptional activators, modifications in the regulatory regions of a gene such that expression is reduced/enhanced, or modifications in the coding region of a gene such that the enzymatic activity of the corresponding protein is increased/decreased, the specification is completely silent regarding the nature of such modifications, other than disclosing overexpression of a gene by increasing its copy number as a method to increase intracellular activity, and inactivating deletions as a method to block/reduce/inactivate a protein. The claims require the enhancement/attenuation/blockage of an extremely large number of proteins which the specification fails to identify either functionally or structurally (i.e., any gene of the biosynthetic pathway of L-lysine, or any pathway which would lead to reduction of L-lysine formation). While the claims require the enhancement/overexpression/attenuation of several genes (listed in claims 4 and 5), the specification fails to disclose a structure which is representative of the extremely large number of genes encompassed by the claims.

In addition to a genus of modifications which have not been disclosed, the claims require a genus of nucleic acids which are structurally unrelated. A sufficient written description of a genus of polynucleotides may be achieved by a recitation of a representative number of polynucleotides defined by

their nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of nucleic acids required in the claimed invention. There is no information as to a correlation between the structures disclosed/known in the art and the required activities. Furthermore, while one could argue that the structures of known nucleic acids are representative of all members of the genus of nucleic acids required, such that the claimed invention is adequately described, it is noted that the art teaches several examples of how even small variations in structure can lead to functional variation. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms β-ketoacyl ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with activity has been provided, one cannot reasonably conclude that the known structures are representative of all the nucleic acids required in the claimed invention.

Due to the fact that the specification only discloses a single species of the coryneform bacterium required in the claimed method, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

17. Claims 1-12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for the production of L-lysine which requires the cultivation of a *C. glutamicum* DSM13994 mutant which is growth-inhibited by 4-hydroxydiaminopimelic acid and has been labeled as DSM13994_Hdap_s, does not reasonably provide enablement for (1) a process for the

production of L-lysine with any L-lysine coryneform bacterium which is growth-inhibited by (i) any diaminopimelic acid analog, or (ii) 4-fluorodiaminopimelic acid, 4-hydroxydiaminopimelic acid, 4-oxodiaminopimelic acid, or 2,4,6-triaminopimelic acid, or (2) a process as described in (1) wherein said bacterium is modified in any way to increase/decrease the intracellular activity of proteins/enzymes which are part of the biosynthetic pathway of L-lysine or which inhibit L-lysine synthesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 1-12 and 14 are so broad as to encompass (1) a process for the production of L-lysine comprising cultivating a L-lysine producing coryneform bacterium, *C. glutamicum* cell or *Brevibacterium* cell whose growth is inhibited in the presence of (i) any diaminopimelic acid analogue, (ii) 4-fluorodiaminopimelic acid, 4-hydroxydiaminopimelic acid, 4-oxodiaminopimelic acid, or 2,4,6-triaminopimelic acid, and (2) a process as described in (1) wherein the coryneform bacterium is modified in any way such that (i) the intracellular activity of any protein associated with the biosynthesis of L-lysine is increased, (ii) the intracellular activity of any feedback-resistant aspartate kinase, dihydrodipicolinate synthase, glyceraldehyde-3-phosphate dehydrogenase, pyruvate carboxylase, glucose-6-phosphate dehydrogenase, lysine export protein, zwa1 protein, diaminopimelic acid decarboxylase, sigma factor C, triose phosphate isomerase, and/or 3-phosphoglycerate kinase is increased, (iii) any

metabolic pathway associated with reducing the formation of L-lysine is blocked, or (iv) the intracellular activity of the gene product of the pck, pgi, deaD, citE, menE, mikE17, poxB, and/or zwa2 gene is reduced or eliminated. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation and Claim Rejections under 35 USC 112, first paragraph, written description, for discussion of scope.

The enablement provided is not commensurate in scope with the claims due to the potentially large number of modifications of unknown nature required in any coryneform bacterium such that it would be growth-inhibited by any diaminopimelic acid analogue and produce L-lysine, as well as the extremely large number of genes of unknown structure and/or function required to enhance synthesis of L-lysine, and the unknown methods which would allow (1) increased intracellular activity of those proteins which enhance synthesis of L-lysine, and (2) decreased/reduced/attenuated intracellular activity of those proteins which inhibit synthesis of L-lysine. In the instant case, the specification enables a process for the production of L-lysine which requires the cultivation of a *C. glutamicum* DSM13994 mutant which is growth-inhibited by 4-hydroxydiaminopimelic acid and has been labeled as DSM13994_Hdap_s.

The amount of direction or guidance presented and the existence of working examples. The specification discloses the production of L-lysine by cultivating an L-lysine *C. glutamicum* strain which is growth-inhibited by 4-hydroxydiaminopimelic acid (labeled as DSM13994_Hdap_s), as a working example. However, the specification fails to disclose which modifications are required in any coryneform bacterium such that it would be growth-inhibited by any diaminopimelic acid analog, 4-fluorodiaminopimelic acid, 4-hydroxydiaminopimelic acid, 4-oxodiaminopimelic acid, or 2,4,6-triaminopimelic acid, and is able to produce L-lysine. Furthermore, the specification fails to disclose(1) the structure and/or function of proteins which enhance L-lysine synthesis, (2) the structure and/or function of proteins which inhibit L-lysine synthesis, and (3) other methods to increase the intracellular

activity of a protein/enzyme, or other methods to decrease/switched off/attenuate the intracellular activity of a protein/enzyme.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. There is no teaching in the specification or the art as to which are the modifications required in any coryneform bacterium such that it would be growth-inhibited by any diaminopimelic acid analogue, and still would be able to produce L-lysine. The specification is silent in regard to the genes which are associated with growth inhibition by diaminopimelic acid analogues and how they have to be modified to obtain growth inhibition.

The nucleotide sequence of a nucleic acid encoding a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any nucleic acid encoding a protein which enhances L-lysine synthesis, or a protein which inhibits L-lysine synthesis. Similarly, neither the specification nor the art provide any teaching or guidance as to the structural modifications required in any gene encoding a protein which enhances/inhibits L-lysine synthesis such that its intracellular activity is increased/decreased, such as modifications in the regulatory regions to increase/decreased expression, or modifications in the coding region which would result in a variant with increased/decreased activity. Also, there is no disclosure of chemical/biological agonists/inhibitors or transcriptional activators.

The art clearly teaches the high level of unpredictability with regard to the effect of structural changes in a protein's activity when no guidance/knowledge as to which amino acids are required for activity has been provided. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of

effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polynucleotide were known in the art at the time of the invention, as well as methods to overexpress a gene or to obtain inactivating deletions, it was not routine in the art to screen by a trial and error process for (1) all modifications in coryneform bacteria which would result in L-lysine production and growth inhibition by any diaminopimelic acid analogue, (2) an essentially infinite number of mutations within expression control elements of any gene encoding a protein which enhances/inhibits L-lysine synthesis to obtain higher/lower expression, (3) any chemical/biological compound which would increase/decrease a protein's intracellular activity, or (4) any mutation in the coding region of a gene which would result in a variant having increased/decreased activity. In the absence of (1) a correlation between structure and function, (2) some guidance as to which are the structural changes within the expression control elements of any gene which would result in increased/reduced expression, (3) some guidance as to the structural changes required in any protein to increase/decrease intracellular activity, or (4) some guidance as to what is required in any compound which increases/decreases activity or expression, one of skill in the art would have to (1) test an extremely large number of coryneform bacteria to determine which ones are growth-inhibited by any diaminopimelic acid analogues, and determine which ones produce L-lysine, (2) determine the structure and/or function of any protein which enhances/inhibits L-lysine synthesis, (3) test

an essentially infinite number of modifications, including modifications within the expression control elements of a gene to determine which ones would result in increased/decreased expression, and/or (4) test an essentially infinite number of compounds/biologicals to determine which ones enhance/inhibit a protein's intracellular activity.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

18. It is noted that if the claims are further amended to refer specifically to the *C. glutamicum* strain labeled DSM13994_Hdap_s, an enablement rejection would be introduced if there is no evidence of a biological deposit in accordance with 37 CFR 1.801-1.809. If amended, the strain would be essential to the claimed invention. The strain has not been disclosed as obtainable by a repeatable method or otherwise being readily available to the public. The enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the strain. If a deposit has been made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement.

If a deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an

affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

a. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;
b. upon granting of the patent the strain will be available to the public under the conditions specified in 37 CFR 1.808;
c. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
d. the deposit will be replaced if it should ever become unviable.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

20. Claims 1-12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Farwick et al. (U.S. Publication No. US 20030113879, U.S. Application No. 09/770688 filed June 6, 2001).

Claims 1-12 and 14 are directed to a process for the production of L-lysine comprising cultivating a L-lysine producing *C. glutamicum* or *Brevibacterium* strain whose growth is inhibited in the presence of a diaminopimelic acid analogue selected from the group consisting of 4-fluorodiaminopimelic acid, 4-hydroxydiaminopimelic acid, 4-oxodiaminopimelic acid, and 2,4,6-triaminopimelic acid, wherein (1) at least one gene of the biosynthetic pathway of L-lysine is enhanced, (2) at least one of the pathways associated with reducing the formation of L-lysine is partially blocked, (3) one or more of the genes selected from the group consisting of lysC, dapA, gap, pyc, zwf, lysE, zwa1, lysA, sigC, tpi, and pgk is overexpressed or enhanced, or (4) one or more of the genes selected from the group consisting of pck, pgi, deaD, citE, menE, mikE17, poxB, and zwa2 is attenuated.

Farwick et al. teach the production of L-lysine by culturing L-lysine producing *C. glutamicum* and *Brevibacterium* strains (page 2, paragraphs [38]-[50]), wherein the gene encoding citrate lyase E (citE) is inactivated by an insertional deletion (page 4, paragraphs [71], [79]; Examples 4-5), and wherein additional genes are overexpressed, including the dapA, gap, tpi, pgk, zwf, lysC, lysE, and zwa1 genes. These genes would be considered genes of the biosynthesis pathway of L-lysine. Farwick et al. also teach that in addition to inactivating the citE gene, other genes are inactivated, including the pck, pgi, poxB, and zwa2 genes. The products encoded by these genes would be considered inhibitors of L-lysine production as they would divert metabolites away from the L-lysine biosynthesis pathway. One of skill in the art would expect any diaminopimelic acid analog to be detrimental to cell growth at a certain concentration because the analog would compete against diaminopimelic acid (endogenous substrate) for the enzymes which catalyze the conversion of diaminopimelic acid to the precursors of L-lysine and/or peptidoglycan. As a result, one would expect a reduction in the precursors of L-lysine and/or peptidoglycan, both being essential metabolites for normal cell function. Thus, for the reasons set forth above, while not specifically stated, the strains of Farwick et al. would be growth-inhibited by any diaminopimelic acid analog at a particular concentration. The process of claims 1-12 and 14 does not require the presence of any diaminopimelic acid analog in the medium, nor do they recite any limitation as to the level of diaminopimelic acid analog associated with growth inhibition of the recited coryneform bacteria (e.g., inhibited by X amount of diaminopimelic acid analog). Thus, the teachings of Farwick et al. anticipate the instant claims as written.

21. Claims 1-12 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Bathe et al. (WO 2004/013340 filed July 10, 2003).

Claims 1-12 and 14 are directed to a process for the production of L-lysine comprising cultivating a L-lysine producing *C. glutamicum* or *Brevibacterium* strain whose growth is inhibited in the presence of

a diaminopimelic acid analogue selected from the group consisting of 4-fluorodiaminopimelic acid, 4-hydroxydiaminopimelic acid, 4-oxodiaminopimelic acid, and 2,4,6-triaminopimelic acid, wherein (1) at least one gene of the biosynthetic pathway of L-lysine is enhanced, (2) at least one of the pathways associated with reducing the formation of L-lysine is partially blocked, (3) one or more of the genes selected from the group consisting of lysC, dapA, gap, pyc, zwf, lysE, zwa1, lysA, sigC, tpi, and pgk is overexpressed or enhanced, or (4) one or more of the genes selected from the group consisting of pck, pgi, deaD, citE, menE, mikE17, poxB, and zwa2 is attenuated. Bathe et al. teach a process for the production of L-lysine wherein said process requires cultivating an L-lysine producing *C. glutamicum* or *Brevibacterium* strain whose growth is inhibited in the presence of a diaminopimelic acid analogue selected from the group consisting of 4-fluorodiaminopimelic acid, 4-hydroxydiaminopimelic acid, 4-oxodiaminopimelic acid, and 2,4,6-triaminopimelic acid, wherein (1) at least one gene of the biosynthetic pathway of L-lysine is enhanced, (2) at least one of the pathways associated with reducing the formation of L-lysine is partially blocked, (3) one or more of the genes selected from the group consisting of lysC, dapA, gap, pyc, zwf, lysE, zwa1, lysA, sigC, tpi, and pgk is overexpressed or enhanced, or (4) one or more of the genes selected from the group consisting of pck, pgi, deaD, citE, menE, mikE17, poxB, and zwa2 is attenuated (page 2, line 23-page 3, line 25; page 4, line 13-page 5, line 15; page 6, lines 22-29; page 7, line 4-page 8, line 26; Examples 1-2). Thus, the teachings of Bathe et al. anticipate the instant claims as written.

22. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Double Patenting

23. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ...

may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

24. Claims 1-12 and 14 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-12 and 14 of copending Application No. 10/630740. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

25. No claim is in condition for allowance.

26. The cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources.

27. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
June 24, 2006